

Predicting acute toxicity hazard in the absence of experimental data: Case studies from the alternatives assessment paradigm

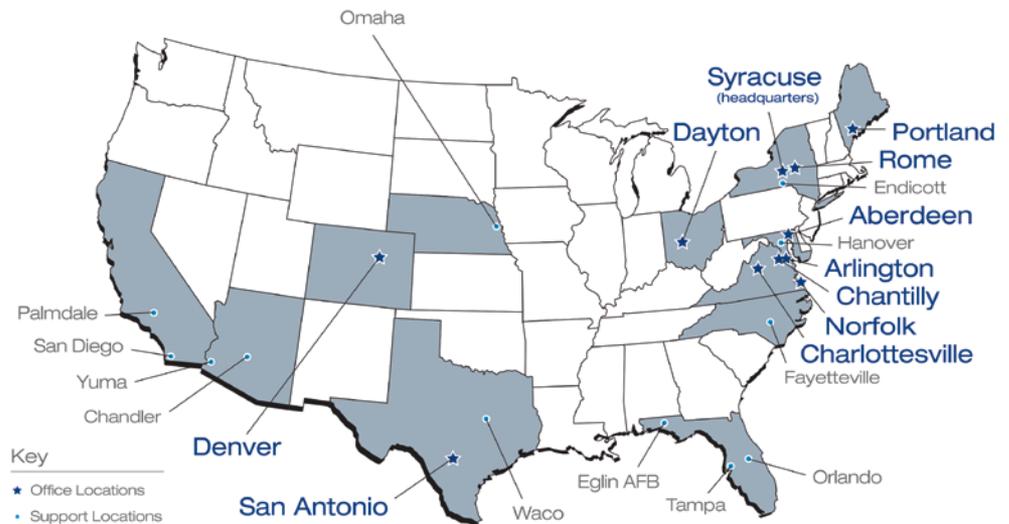
Jay Tunkel

SRC, Inc. Syracuse, New York, USA



Who Are These Guys?

- ▶ Founded in 1957 as Syracuse University Research Corporation as a not-for-profit organization by the NY State Board of Regents
- ▶ Became Syracuse Research Corporation in 1976, and SRC, Inc. in 2009



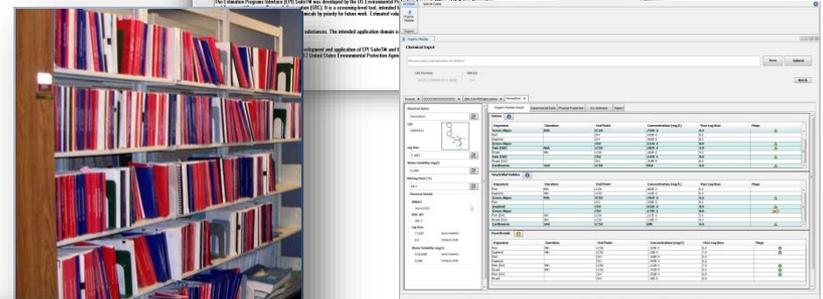
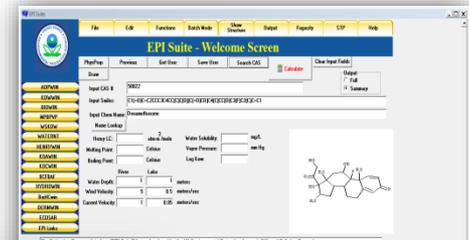
Environmental Health Analysis Group

➤ EPA

- New Chemicals program (>25,000 PMNs assessed)
- Safer Choice/DfE (supported AAs, SPLP, and SCIL since their inception)
- IRIS

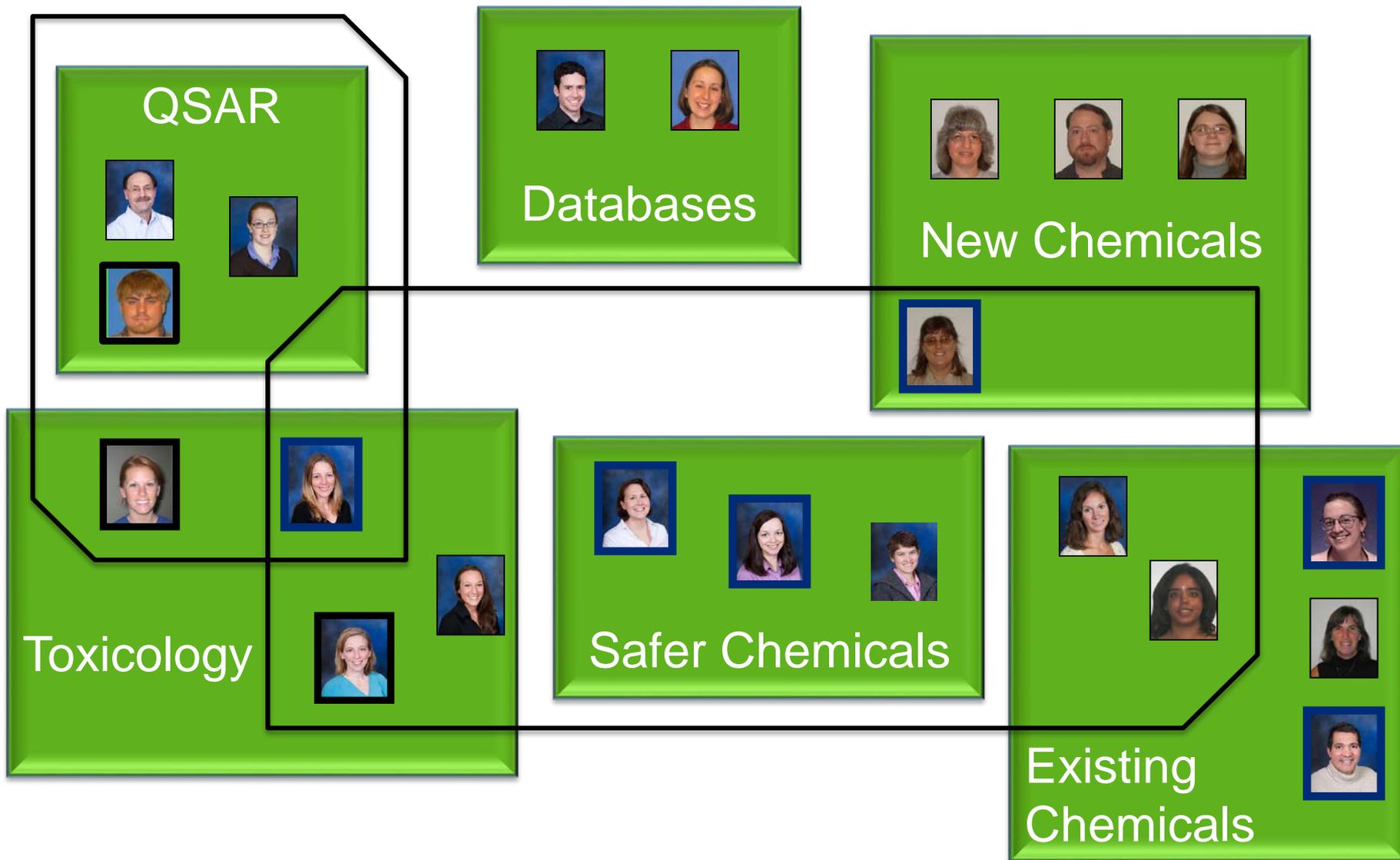
➤ Other Government

- NLM/NIH – HSDB
- CDC/ATSDR Toxicological profiles
- OSHA – PELs
- State Agencies
- DoD





The Chemical Hazard Assessment Group

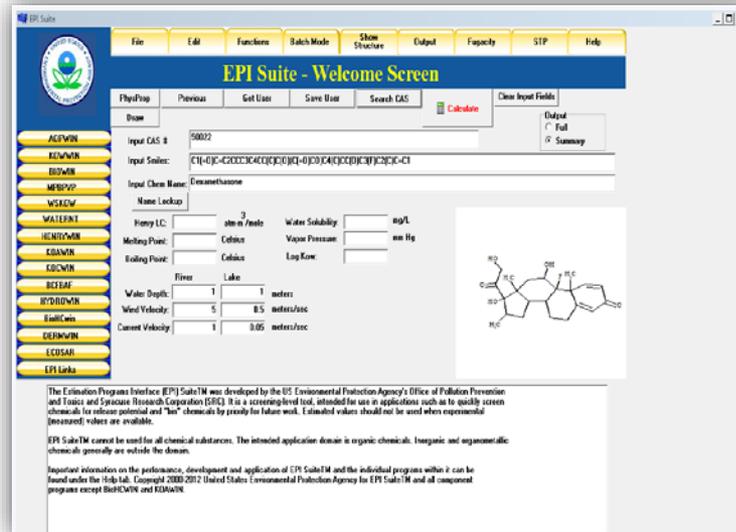


Disclaimer

- All chemical information presented herein is available in the public domain



- Views expressed are those of the author alone



The screenshot shows the EPI Suite software interface. At the top, there is a menu bar with options: File, Edit, Functions, Batch Mode, Show Structure, Output, Fugacity, STP, and Help. Below the menu bar is the title 'EPI Suite - Welcome Screen'. The main area contains several input fields and buttons. On the left, there is a vertical list of chemical names: ALCHLN, KEMWIN, BIOWIN, MROVP, WSKOW, WALKER, HENLOWIN, EDWIN, EDCWIN, BCFBAF, HYDROWIN, EcolCwin, DEHMWIN, LCCSAR, and EPI Links. The main input area includes fields for 'Input CAS #', 'Input SMILES', 'Input Chem Name', 'Name Lookup', 'Henry LC', 'Melting Point', 'Boiling Point', 'Water Depth', 'Wind Velocity', and 'Current Velocity'. There are also buttons for 'Previous', 'Get List', 'Save User', 'Search CAS', 'Calculate', and 'Clear Input Fields'. A 'Output' section on the right has radio buttons for 'Full' and 'Summary'. A chemical structure diagram is shown on the right side of the interface. At the bottom, there is a disclaimer text.

The Estimation Programs Interface (EPI) Suite™ was developed by the US Environmental Protection Agency's Office of Pollution Prevention and Toxicity and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in applications such as to quickly screen chemicals for release potential and "hot" chemicals for priority for future work. Estimated values should not be used when experimental (measured) values are available.

EPI Suite™ cannot be used for all chemical substances. The intended application domain is organic chemicals. Inorganic and organometallic chemicals generally are outside the domain.

Important information on the performance, development and application of EPI Suite™ and the individual programs within it can be found under the Help tab. Copyright 2002-2012 United States Environmental Protection Agency for EPI Suite™ and all component programs except BIOWIN and KEMWIN.

PBT Characteristics

Persistence			
	Low	Moderate	High
Half-life	<60 days	60-180 days	>180 days

QSAR?

✓

Bioaccumulation			
	Low	Moderate	High
BCF	>1,000	1,000-5,000	>5,000

✓

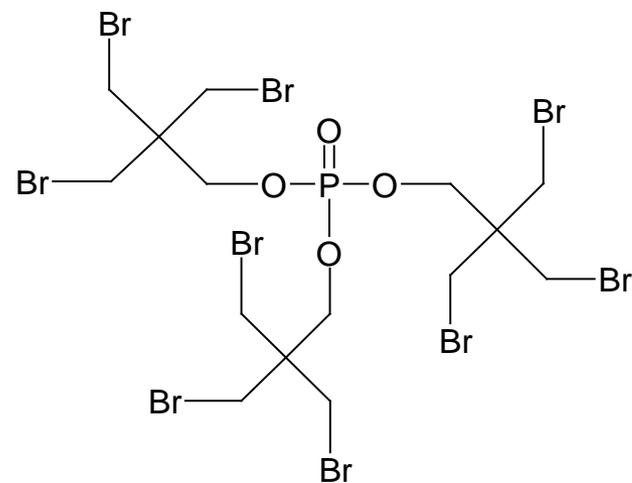
Aquatic Toxicity			
	Low	Moderate	High
Acute	>100 mg/L	1-100 mg/L	<1 mg/L
Chronic	>10 mg/L	0.1-10 mg/L	<0.1 mg/L

✓

✓

Hierarchy for Predicting HH Hazard

- ▶ Analog
 - Data available on closely related compounds
- ▶ Read Across
 - Data available for multiple analogs
- ▶ Chemical class
 - Local effects
 - Functional groups
 - Mechanistic basis
- ▶ Also considered...
 - Metabolites
 - Reaction products (e.g., hydrolysis)



Predicting Concern, Includes **LOW** Toxicity

Company	Chemical ¹	% in Formulation ³	Human Health Effects						Ecotoxicity		Environmental		
			Cancer Hazard	Skin Sensitizer	Reproductive	Developmental	Neurological	Systemic	Genotoxicity	Acute	Chronic	Persistence	Bioaccumulation
Albemarle	ANTIBLAZE 180 and ANTIBLAZE 195												
	Tris(1,3-dichloro-2-propyl)Phosphate CAS # 13674-87-8	95%	M	L	M	M	L	M	M	M	M	M	L
Albemarle	ANTIBLAZE 182 and ANTIBLAZE 205												
	Proprietary A Chloroalkyl phosphate (1)		M	L	M	M	L	M	M	M	M	M	L
	Proprietary B Aryl phosphate		L	L	M*	M*	M	M*	L	H	H	L	M
	Triphenyl Phosphate CAS # 115-86-6		L	L	L	L	L	M	L	H	H	L	L
Albemarle	ANTIBLAZE V500												
	Proprietary C Chloroalkyl phosphate (2)		M	M	M*	M*	L	M	L	M	M	M	L
	Proprietary B Aryl phosphate		L	L	M*	M*	M	M*	L	H	H	L	M
	Triphenyl Phosphate CAS # 115-86-6		L	L	L	L	L	M	L	H	H	L	L



DfE Acute Criteria

Route	VH	H	M	L (P/F)
Oral, LD ₅₀ (mg/kg bw)	≤50	>50-300	>300-2,000	>2,000
Dermal, LD ₅₀ (mg/kg bw)	≤200	>200-1,000	>1,000-2,000	>2,000
Inhalation, LC ₅₀ (vapor/gas; mg/L)	≤2	>2-10	>10-20	>20
Inhalation, LC ₅₀ (dust/mist/fumes; mg/L/d)	≤0.5	>0.5-1	>1.0-5	>5

We Are Modelers



EPI Suite™

EPI Suite - Welcome Screen

File Edit Functions Batch Mode Show Structure Output Property STP Help

Draw

Input CAS #: 50022

Input SMILES: C1=O=C2CCC3C4CC(C)C(O)C(=O)CO)C4(C)CC(O)C3(F)C2(C)C=C1

Input Chem Name: Dexamethasone

Name Lookup: Dexamethasone

Heavy LC: liters of water Water Solubility: mg/L

Melting Point: Celsius Vapor Pressure: mm Hg

Boiling Point: Celsius Log Kow:

River: Lake:

Water Depth: 1 1 meters

Wind Velocity: 5 8.5 meters/sec

Current Velocity: 1 0.05 meters/sec

The Evaluation Program Interface (EPI) Suite™ was developed by the US Environmental Protection Agency's Office of Pollution Prevention and Toxicity and Syracuse Research Corporation (SRC). It is a screening-level tool, intended for use in applications such as to quickly screen chemicals for release potential and "hot" chemicals by priority for future work. Estimated values should not be used when experimental (measured) values are available.

EPI Suite™ cannot be used for all chemical substances. The intended application domain is organic chemicals, inorganic, and organometallic chemicals.

Report and saved results programs v...



EPI Suite

Submit Draw

DEXAMETHASONE

Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, (11 beta, 16 alpha.) -
• C₂₂H₂₉F₃O₅

CAS RN: 50-02-2

SMILES:
C1(=O)C=C2CCC3C4CC(C)C(O)C(=O)CO)C4(C)CC(O)C3(F)C2(C)C=C1

Show Key Change Theme

log K_{ow} 1.72 1.94

log BCF 0.80

Chemical Input

Please enter CAS Number or SMILES

CAS Number: 50022 SMILES: C1=O=C2CCC3C4CC(C)C(O)C(=O)CO)C4(C)CC(O)C3(F)C2(C)C=C1

Draw Submit

Batch

File Edit Functions Batch Mode Show Structure Output Property STP Help

Chemical Name: Dexamethasone

Chemical Name: Dexamethasone

Operation	Duration	End Point	Concentration (mg/L)	Flow Log Row	Flags
Screen Algae	96h	LC50	2400-2	0.4	
Fish	96h	LC50	100-2	0.1	
Daphnia	96h	LC50	100-2	0.1	
Screen Algae	96h	EC10	1430-1	0.0	
Fish (96h)	96h	LC50	380-1	0.0	
Fish (96h)	96h	LC50	250-1	0.1	
Fish (96h)	96h	LC50	140-1	0.0	
Fish (96h)	96h	LC50	300-1	0.1	
Earthworms	14d	LC50	90-0	0.0	

Operation	Duration	End Point	Concentration (mg/L)	Flow Log Row	Flags
Screen Algae	96h	LC50	900-1	0.1	
Daphnia	96h	LC50	100-1	0.1	
Screen Algae	96h	EC10	2900-1	0.4	
Fish	96h	LC50	100-1	0.1	
Daphnia	96h	EC10	4300-1	0.0	
Screen Algae	96h	EC10	4300-1	0.0	
Fish (96h)	96h	LC50	210-1	0.1	
Fish (96h)	96h	LC50	140-1	0.1	
Earthworms	14d	LC50	200	0.0	

Operation	Duration	End Point	Concentration (mg/L)	Flow Log Row	Flags
Fish	96h	LC50	100-1	0.1	
Daphnia	96h	LC50	100-1	0.1	
Fish	96h	EC10	1000-1	0.0	
Daphnia	96h	EC10	1000-1	0.0	
Fish (96h)	96h	LC50	1100-1	0.1	
Fish (96h)	96h	LC50	1100-1	0.1	
Fish (96h)	96h	LC50	1100-1	0.1	
Fish (96h)	96h	LC50	1100-1	0.1	

On the Way to Work....



International QSAR Workshop



Credibility • Purpose • Opportunity



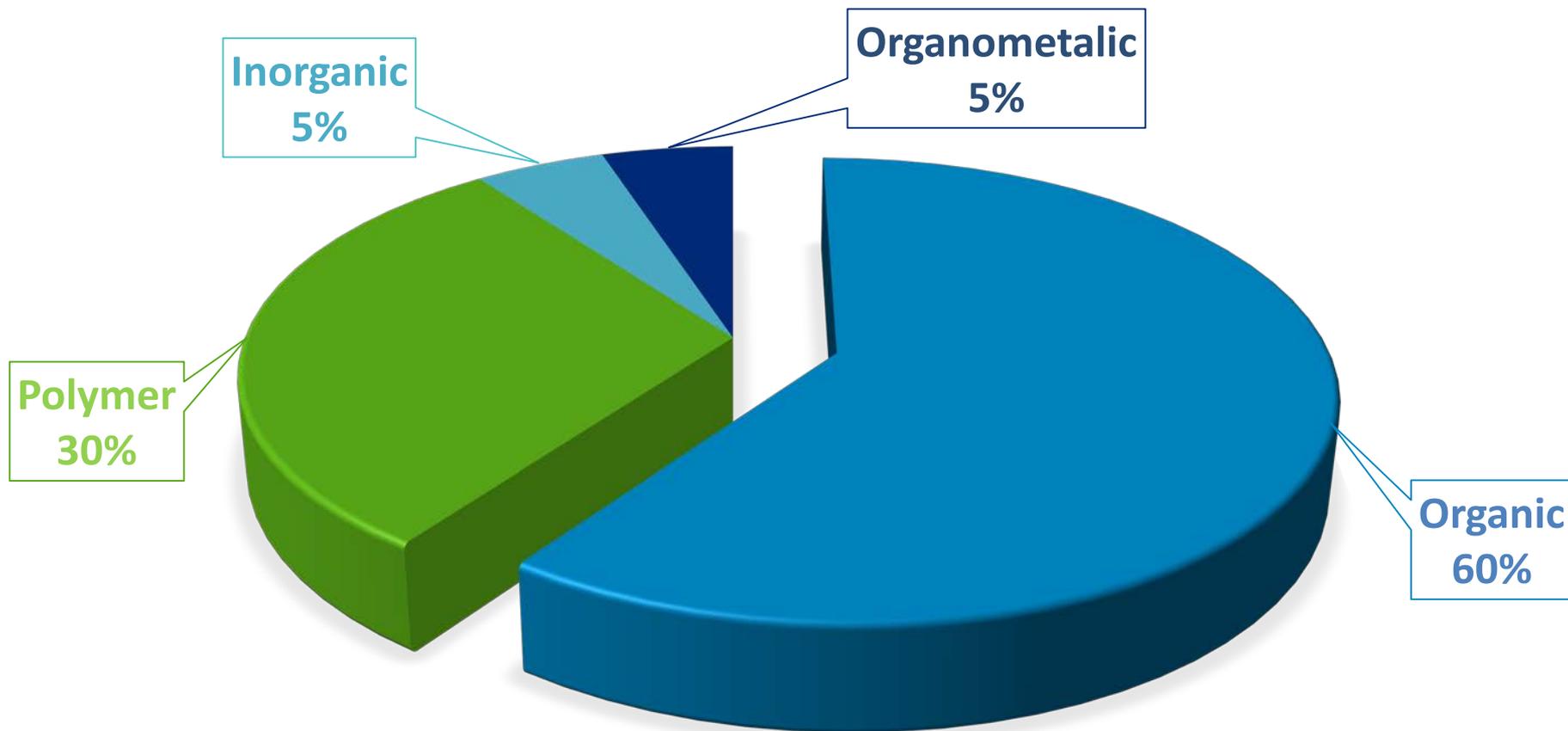
The 13th International

Workshop on QSARs in the Environmental Sciences

June 8th - 12th, 2008 · Syracuse, New York, USA

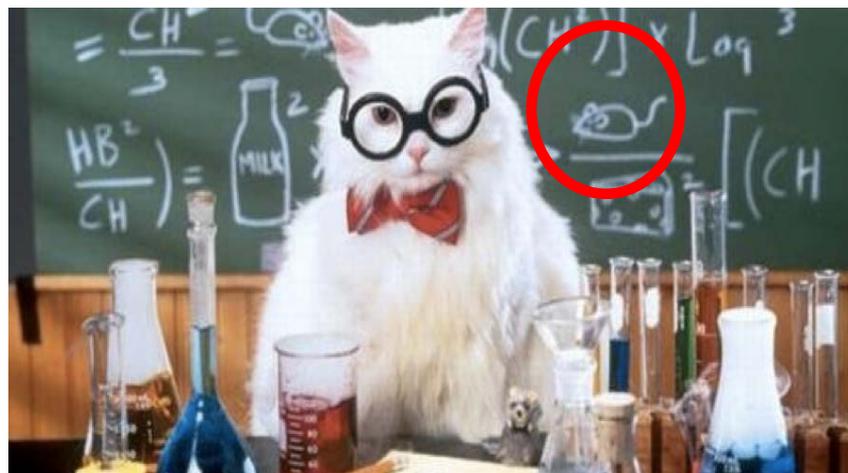
QSAR 2016 ~ June 13th-17th ~ Miami Beach

What About the Dis-Organics?



Perhaps from a Chemist's Perspective

- ▶ Don't forget the importance of Physical/Chemical properties!
- ▶ Mechanistic understanding & verification of:
 - Functional group(s)
 - Mechanism
 - Metabolites
 - Electronic affects
 - Steric demands
 - Initiating event (AOP)
 - Mixtures



Analog Identification Methodology (AIM)

Lookup Structure | Draw Structure | Advanced Options | Report Settings

Lookup by CAS Number or Chemical Name

CAS # or ID: 111762 [Lookup]

Chemical Name: Ethanol, 2-butoxy- [Lookup]

Smiles Notation: O(CCCC)CCO [Load] [Draw]

Chemical Structure

OH

CH₃

Include Pass 2

[User Manual] [Data Sources] [Fragment Library]

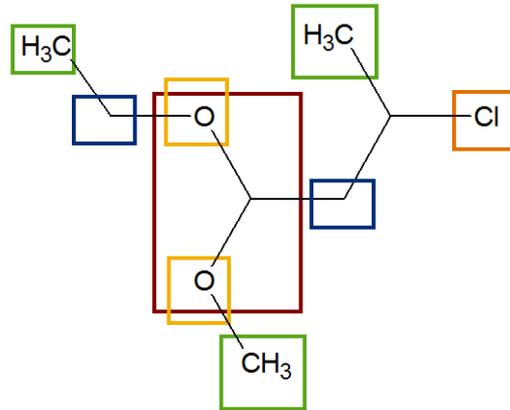
[Find Analogs] [Reset]

Product developed to address stakeholder comments from EPA's Sustainable Futures Initiative

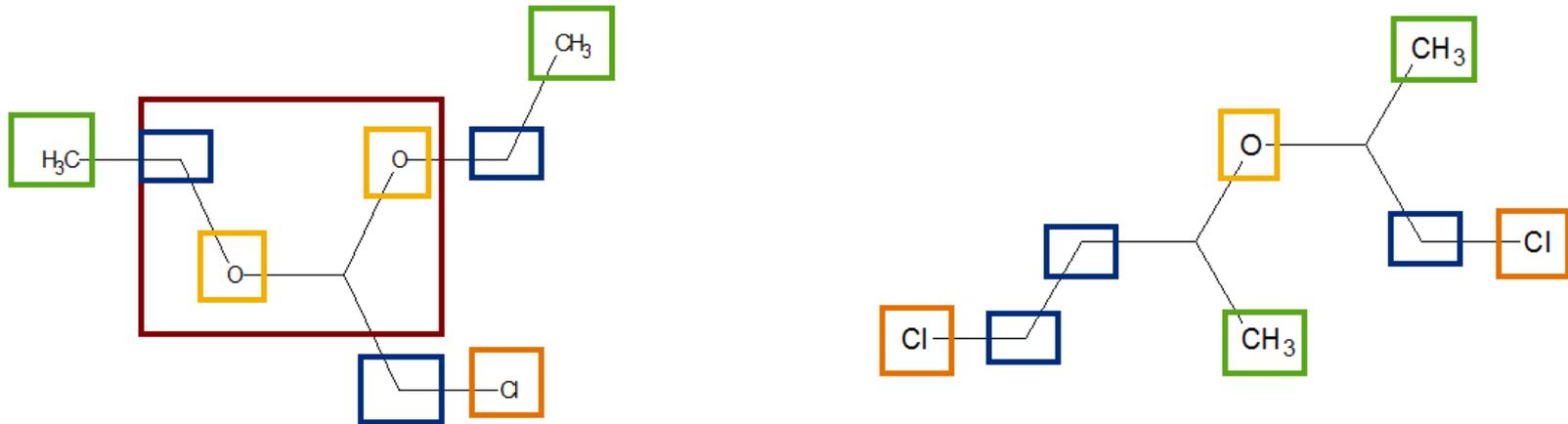
Free download from:
www.epa.gov/oppt/sf/tools/aim.htm

AIM Methodology

Pass 1



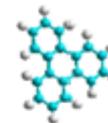
Pass 2



AIM Results



Analog Report For



CAS / ID: 111762
Name: Ethanol, 2-butoxy-
SMILE: O(CCCC)CCO
Options: None
Date: Jul 24, 2015 4:22 PM
78 AIM Results Found



Exact Chemical Match

2-BUTOXYETHANOL [111-76-2]
O(CCCC)CCO

Toxicity Data Available for this Compound

[RTECS](#)

HPV Challenge

[OECD HPV](#)

* May also be located at: [OECD](#)

[ECOTOX](#)

[TSCATS II](#)

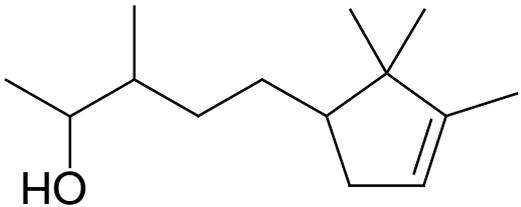
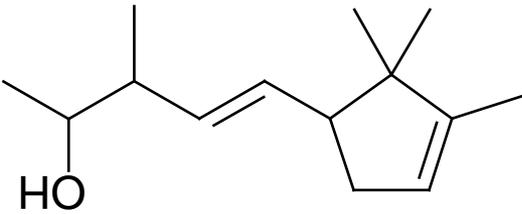
[ACToR](#)

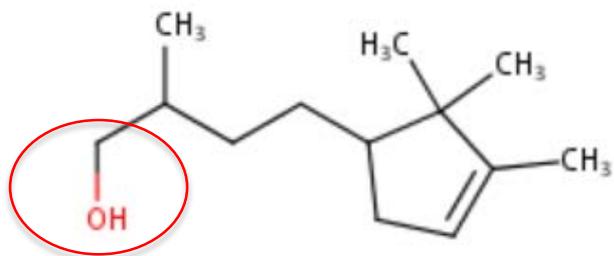
[TSCATS](#)

[IRIS](#)



AIM Example

Name	Sandalore	Ebanol
Structure		
CAS No.	65113-99-7	67801-20-1
Acute toxicity	Pass	Pass

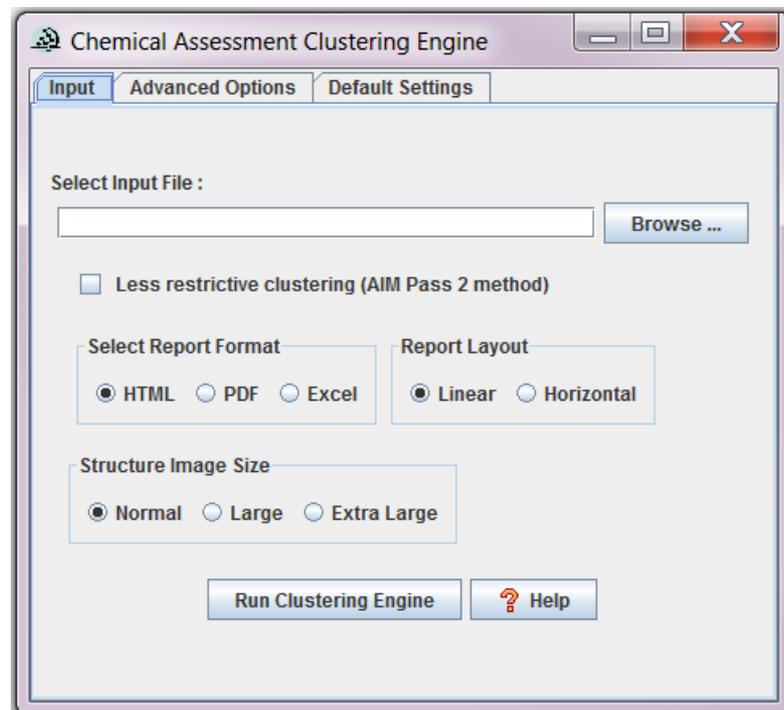


Similarity = 91%

Clustering - ChemACE

▶ ChemACE

- **C**hemical **A**ssessment **C**lustering **E**ngine
- Useful tool for building potential fragrance clusters
- Designed for non-experts
- Clusters chemicals from a user-supplied list based on common fragments
- Methodology defines clusters where members are analogs of each other

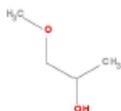


Free download at:

www.epa.gov/oppt/sf/tools/chemace.htm

Clustering (ChemACE)

Cluster: 5

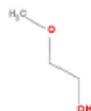


107982

O(CC(O)C)C

1-Methoxy-2-Propanol

None



109864

O(CCO)C

2-Methoxyethanol

None



110805

O(CCO)CC

2-Ethoxyethanol

None



111762

O(CCCC)CCO

2-Butoxyethanol

MOA Evaluation



111900

O(CCOCC)CCO

Diethylene Glycol
Monoethyl Ether

None



112345

O(CCOCCO)CCCC

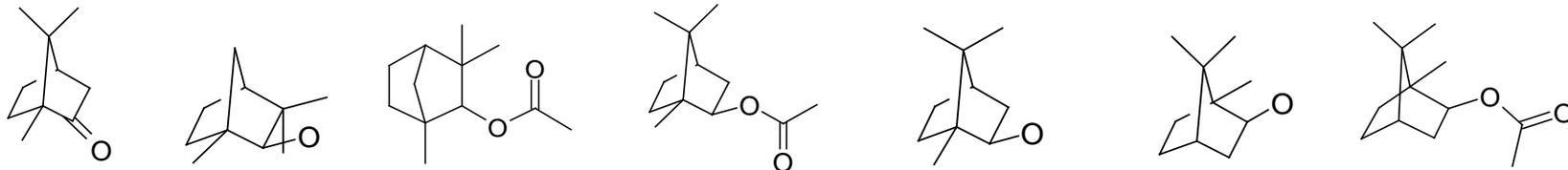
Diethylene Glycol
Monobutyl Ether

None

Case Studies

Organics

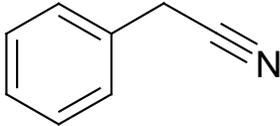
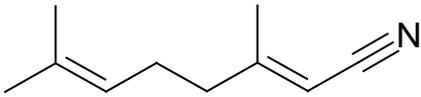
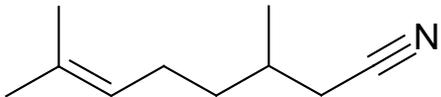
Read Across – Norbornenyl Fragrances

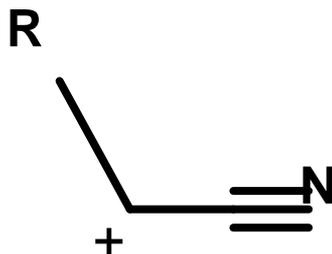


P; B; T	VL; L; M	L; M; M	L; M; H	VL; M; VH	L; M; H	L; L; M	L; M; H
Acute	Fail	Fail (Analog)	Fail (Analog)	Fail (Analog)	Fail (Analog)	Fail (Analog)	Fail (Analog)

Rat (inhalation), LD₅₀ = 0.5 mg/L (ECHA)
 Rat (inhalation-dust), 2-hr, LD₅₀ >10 mg/L (ECHA)
 Mouse (inhalation), 3-hr, LD_{Lo} = 0.4 mg/L (ChemID)

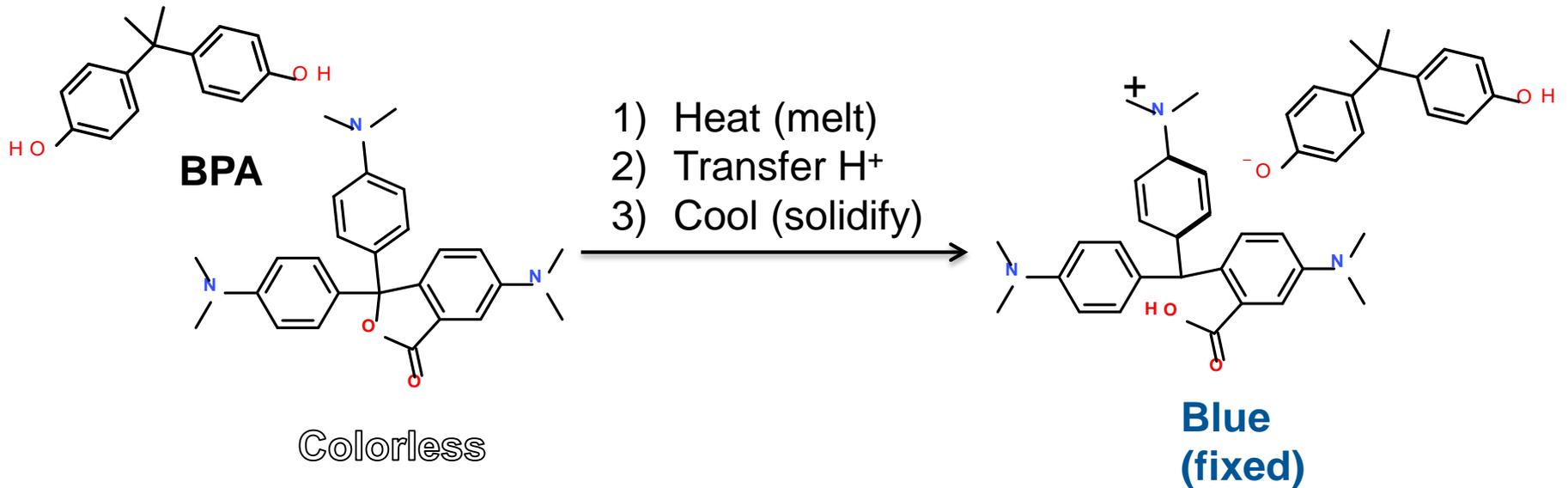
Cyanide Formation from Nitriles

Name	Benzyl cyanide	Geranyl nitrile	Citronellyl nitrile
Structure			
Rat Acute LD ₅₀ (mg/kg)	270	3,100	5,300
Rabbit Acute LD ₅₀ (mg/kg)	270	4,300	No data



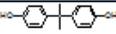
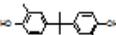
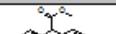
Structural alert for nitriles when stabilized

BPA In Thermal Paper

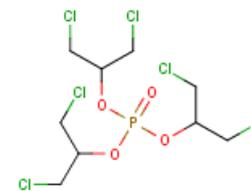
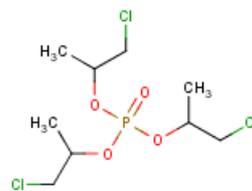
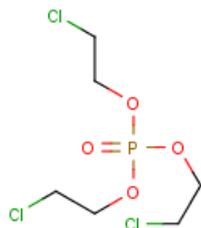


Limited Data – Read Across from BPA

VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard — Endpoints in colored text (VL, L, M, H, and VH) were assigned based on empirical data. Endpoints in black italics (*VL, L, M, H, and VH*) were assigned using values from estimation software and professional judgment.
 § Based on analogy to experimental data for a structurally similar compound.

Structure	Chemical (for TSCA inventory name and relevant trade names see the individual profiles in Section 4.8)	CASRN	Human Health Effects											Aquatic Toxicity		Environmental Fate	
			Acute Toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
	Bisphenol A 2,2-bis(p-hydroxyphenyl)propane	80-05-7	L	M	L	M	H	M	M	M		M	M	H	H	VL	L
	Bisphenol F Bis(4-hydroxyphenyl)methane	620-92-8	L	M	L	M [§]	H [§]	M	H	L		VH	M [§]	M	H	L	L
	Bisphenol C 2,2'-Bis(4-hydroxy-3-methylphenyl)propane	79-97-0	L [§]	M	M	M [§]	H [§]	M	M [§]	M [§]		H [§]	M [§]	H	H	M	M
	MBHA Methyl bis(4-hydroxyphenyl)acetate	5129-00-0	L [§]	M	L [§]	M [§]	H [§]	M	M [§]	L		M [§]	M [§]	H	H	M	L
	BisOPP-A 4,4'-Isopropylidenebis(2-phenylphenol)	24038-68-4	L [§]	M	L [§]	M [§]	H [§]	M	M [§]	M [§]		M [§]	M [§]	L	H	H	M
	Bisphenol AP 4,4'-(1-Phenylethylidene)bisphenol	1571-75-1	L [§]	M	L [§]	M [§]	H [§]	M	M [§]	M [§]		M [§]	M [§]	H	H	H	M
	Substituted phenolic compound, PROPRIETARY #1		L [§]	M	L	M [§]	H [§]	M	M [§]	M [§]		M [§]	M [§]	H	M	M	L
	Substituted phenolic compound, PROPRIETARY #2		L [§]	M	L [§]	M [§]	H [§]	M	M [§]	M [§]		M [§]	M [§]	H	H	H	H

Flame Retardant Alternatives



CASRN

[115-96-8](#)

[13674-84-5](#)

[13674-87-8](#)

Chemical

Tris (2-chloroethyl)
phosphate

Tris (2-chloro-1-
methylethyl)
phosphate

Tris(1,3-dichloro-2-
propyl)phosphate

Molecular Weight

285.49

327.57

430.91

State

Liquid

Liquid

Liquid

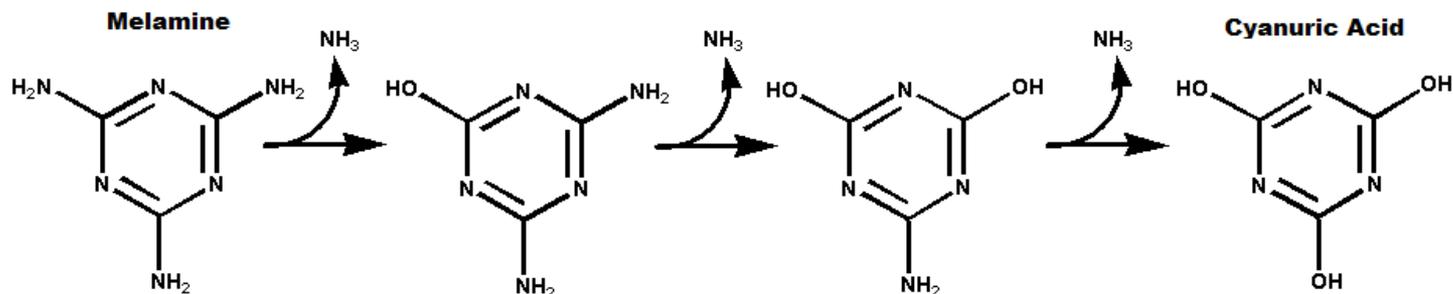
Acute

● 46.4 mg/kg
■ Rat

● 930 mg/kg
■ Rat

● >2000 mg/kg
■ Rat

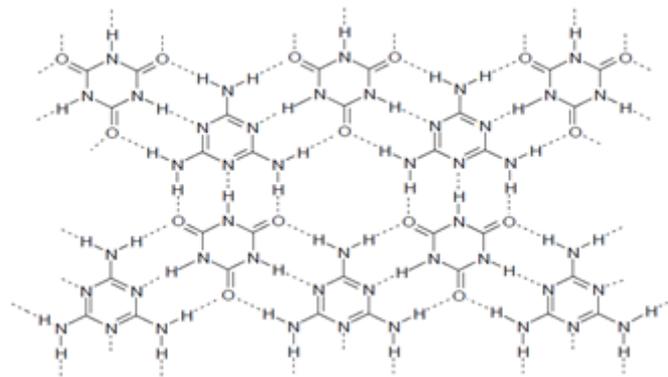
Melamine (TBBPA AA)



Rat LD₅₀ >3,160 mg/kg

Rat LD₅₀ >5,000 mg/kg

Super-strong
hydrogen
Bonds
(pH dependent)

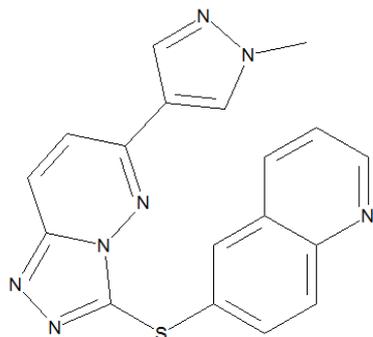


Forms insoluble
crystals in kidneys

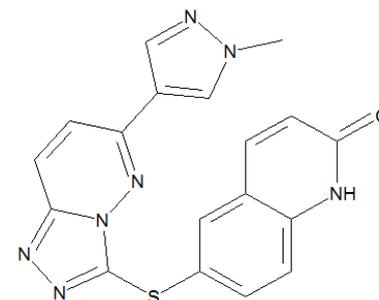
Can QSARs be expected to provide reasonable results for these exceptions?

Don't forget the properties!!!

Phase I clinical testing, all subjects experienced acute renal failure (Mike Bolger Webinar)



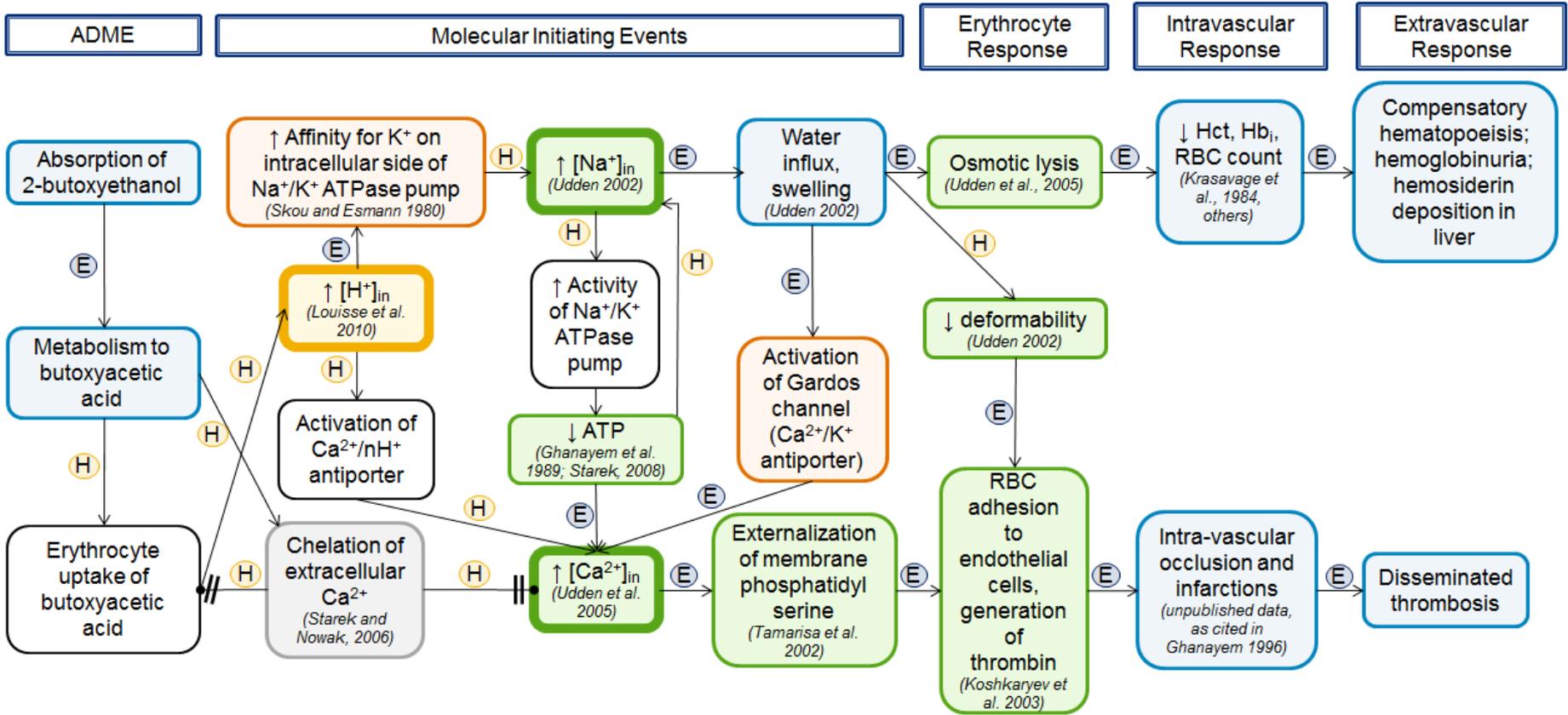
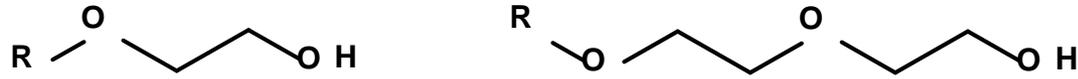
Parent: Soluble



Metabolite: Not Soluble

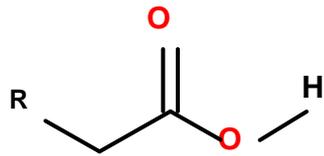
“...physicochemical properties can serve a critical role in alternatives assessment processes...” (NAS 2014; *Tickner, et al. 2015*)

AOP Development

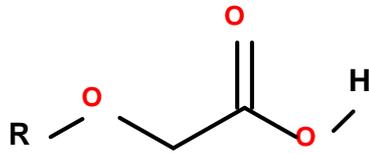
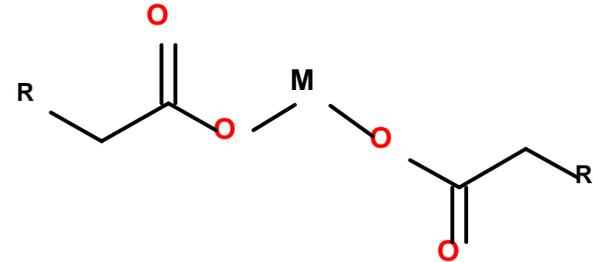


Bold outline: potential molecular initiating event

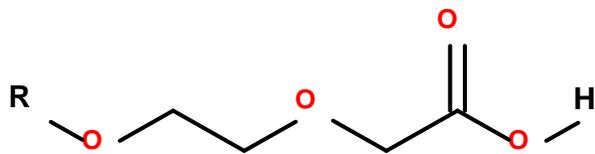
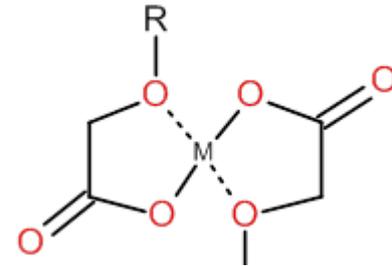
AOP - Oxygen is Important



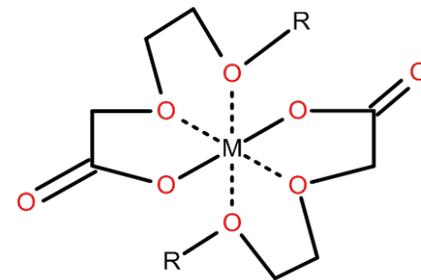
+ Metal cation



+ Metal cation



+ Metal cation



Case Studies

Inorganics, Organometallics and Polymers

Inorganics and Organometallics

Chemicals

- Dicopper chloride trihydroxide
- Copper sulfate pentahydrate
- Dicopper oxide

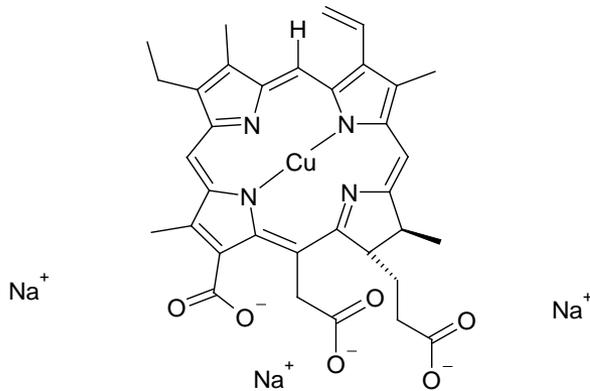
LD₅₀

299-2,006 mg/kg;
in rat and mice

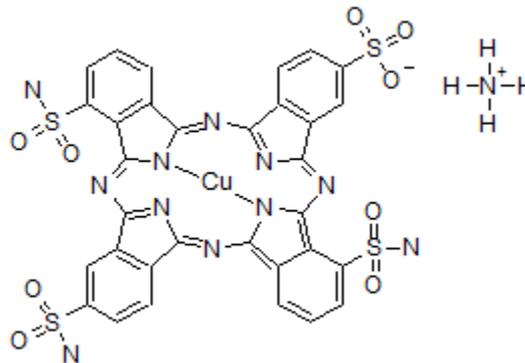
Safer Choice (DfE)

Fail

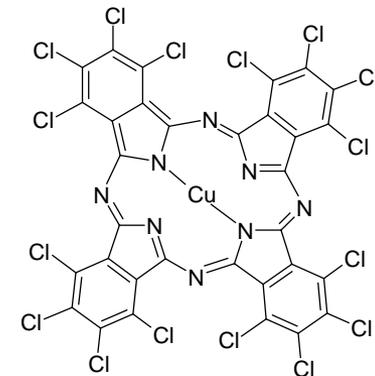
Porphyrins (includes phthalocyanines) – 6 members total, data on 2



Chlorophyll

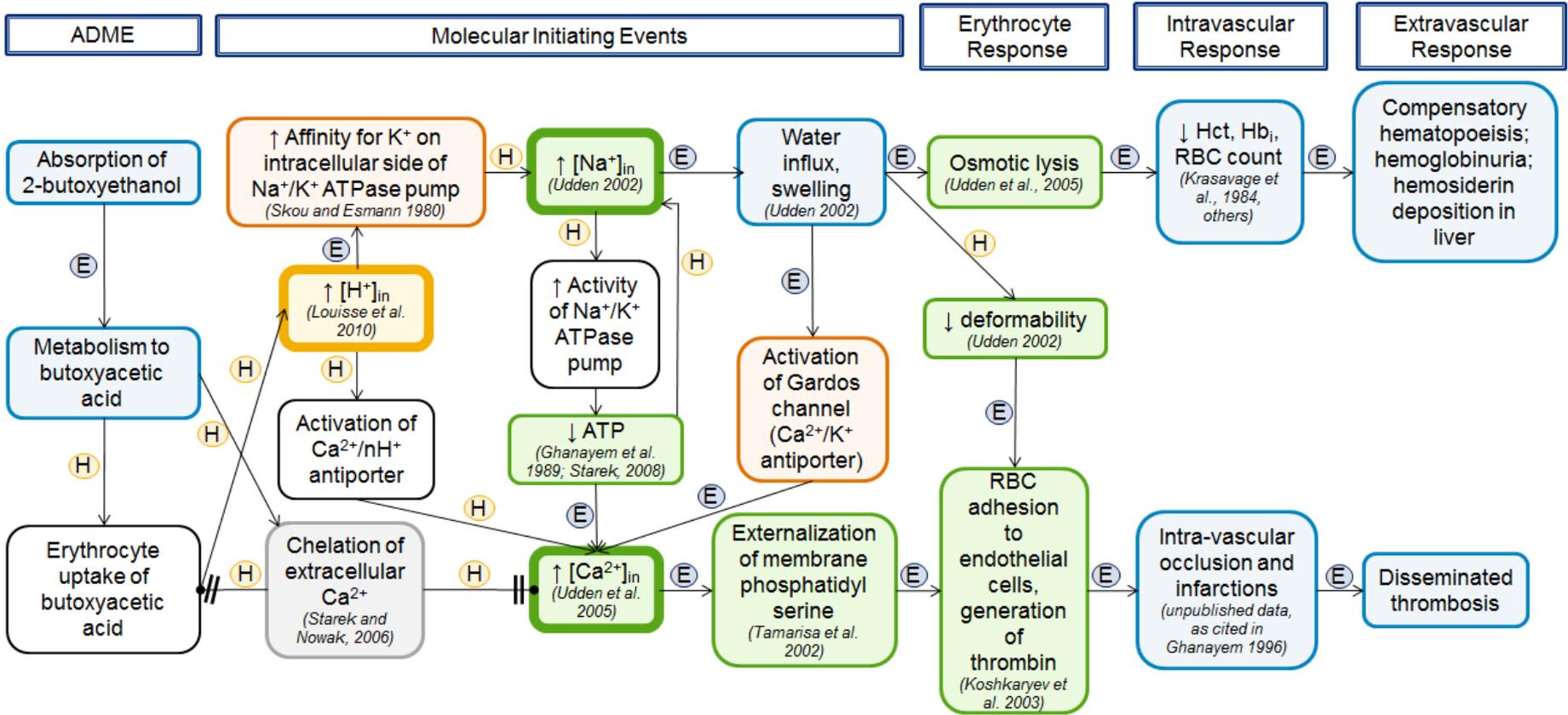
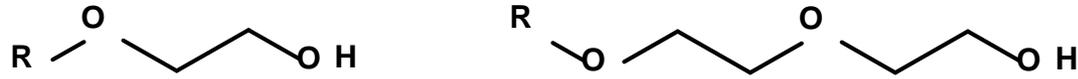


C.I. Pigment Green 7
2,000 mg/kg



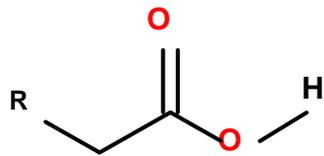
Direct Blue 86
>5,000 mg/kg

AOP Development

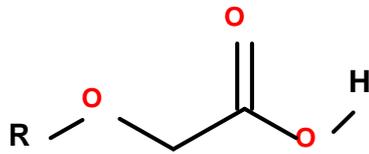
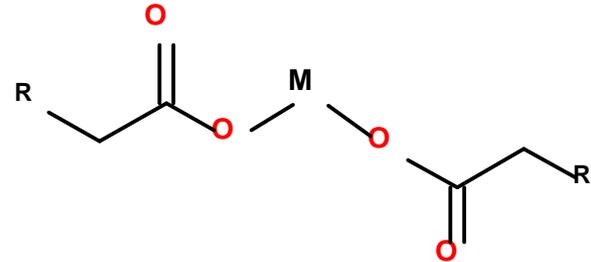


Bold outline: potential molecular initiating event

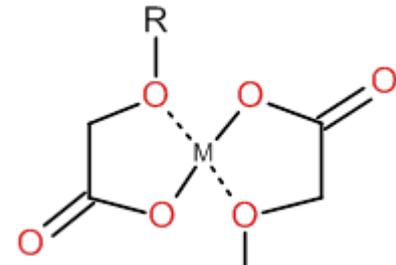
AOP - Oxygen is Important



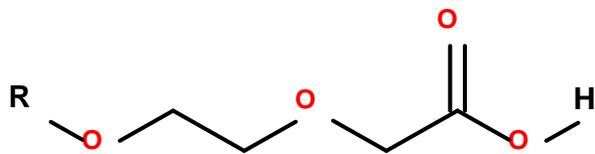
+ Metal cation



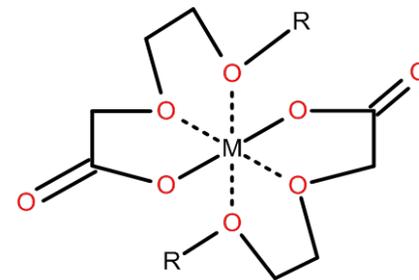
+ Metal cation



AND Enantiomer



+ Metal cation



Predicting Polymer Toxicity

▶ Category 1

- Low molecular weight polymers
- $MW_n < 1,000$

▶ Category 2

- Polymers with high & low MW components
- $MW_n > 1,000$ and $\geq 25\%$ with $MW < 1,000$; $\geq 10\%$ with $MW < 500$

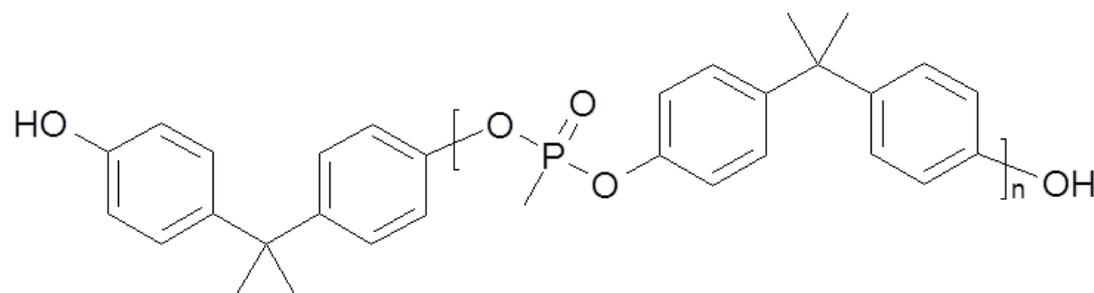
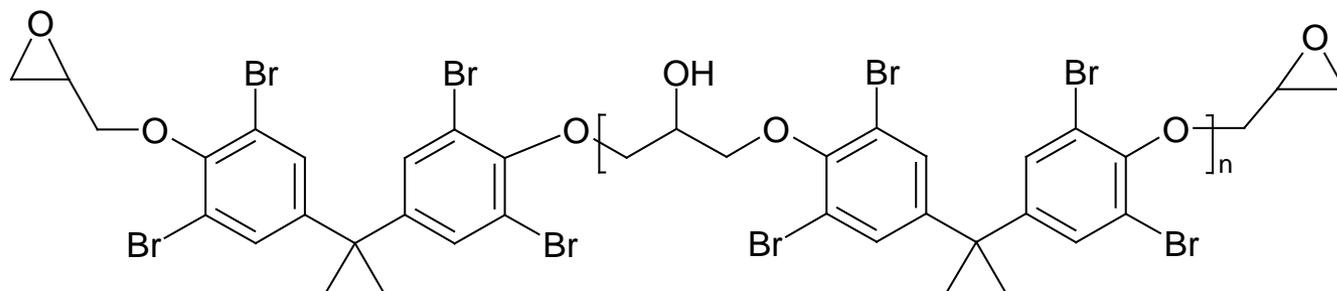
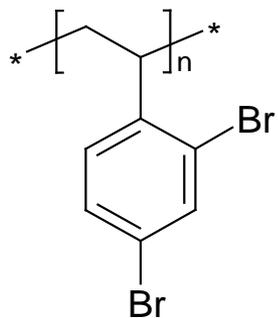
▶ Category 3

- High molecular weight polymers
- $MW_n > 1,000$

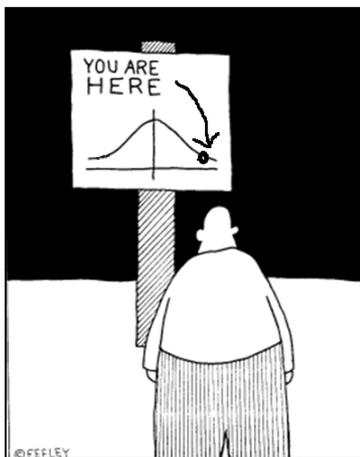
▶ Polymers with potential toxicity are:

- Swellable polymers
- Pendant functional groups of concern (e.g., epoxides)

Polymer Flame Retardant Alternatives



Thank You! Questions?



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